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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/485,421	MAHALINGAM ET AL.	
	Examin r	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 28-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 28-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed on 8/20/03 has been entered. Claims 1, 3-11 have been amended. Claims 28-47 are newly added. Claims 1-11, and 28-47 are pending in the application and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 8/20/03 response would be addressed to the extent that they apply to current rejection.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

The amended specification recites numerous references to previous applications, however, the relationship have not been specified. Appropriate clarification is required. It is noted that the newly submitted paragraph adds new materials to the instant specification based on incorporation by reference to a pending U.S. application.

Accordingly, the present application cannot be a continuation application of the previous application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11 and 28-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because they recite "a nuclear localization sequence fragment of HIV-1 Vpr comprising amino acid sequence 17-36 and/or amino acid sequence 59-84". Since there are multiple sequences for HIV Vpr with minor differences in the chemical structure (See NCBI database list), and the claims do not refer to a particular sequence identifier, it is unclear which sequence the claims encompass, and thus the meets and bounds of the claims are unclear.

Claims 29-31 recite the limitation "said nucleic acid molecule". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, and 7-9 stand rejected under 35 U.S.C. 102(e) as being anticipated by *Cohen et al* (USP 6,043,081).

Applicants argue that Cohen reference fails to discuss a conjugated composition that comprises both a protein and a nucleic acid.

The argument has been fully considered but they are not persuasive. This is because even though *Cohen et al* do not use the term conjugated composition, they do teach different forms of conjugated composition including a chimeric peptide, a nucleic acid encoding the chimeric peptide, and a nucleic acid-Vpr fragment. For example, they teach, "THE TERM THERAPEUTIC AGENT SHOULD BE TAKEN IN A BROAD SENSE SO AS TO ALSO INCLUDE A COMBINATION OF AT LEAST TWO SUCH THERAPEUTIC AGENTS. FURTHER, THE DNA SEGMENTS OR PROTEINS ACCORDING TO." (column 7, lines 10-13, emphasis added). They also recite, "THE ANTI-VIRAL TREATMENT CAN BE EFFECTED THROUGH TRANSFECTION OF A PATIENT'S HEMATOPOIETIC CELLS WITH *A DNA CONSTRUCT HARBORING A VPR/VPX CHIMERIC PROTEIN* AND FOLLOWED BY READMINISTRATION OF THE TRANSFECTED CELLS" (column 5, lines 52-54). Therefore, the rejection stands.

Claims 1, 5-11 stand rejected under 35 U.S.C. 102(b) as being anticipated by

WO9608970.

Applicants argue that there are numerous fragments that can be found in the '970 reference that would not contain the recited sequence fragments, there is not discussion of residues 17-36 and/or 59-84.

The arguments have been fully considered but they are not persuasive for reasons of record and following.

The instant specification defines, "fragment of HIV-1 Vpr protein" is meant to refer to "proteins which are not complete HIV-1 vpr proteins (i.e. full length Vpr protein) but truncated forms", "For example, a protein having amino acids 1-95 of Vpr protein but which is missing amino acid 96 is not identical a full length Vpr protein but is a fragment of Vpr protein" (Specification, page 7, lines 7-13), thus, the claims encompass a fragment of Vpr having amino acids 1-95 of the Vpr. On the other hand, *WO9608970* teaches, "the term functional fragment of Vpr is meant to refer to a fragment of vpr which retains its ability to inhibit cell proliferation and/or induce differentiation and/or induce differentiation of undifferentiated cells and/or prevent lymphocyte activation", "Functional fragment of vpr are at least about 5 amino acids in length derived from vpr" (*WO9608970,* page 11, lines 12-19). There is no limitation at the upper end for the length of the vpr fragment as long as it has the recited function, and has more than 5 amino acids. Clearly, vpr fragment 1-95 is encompassed by the teaching of WO9608970, which fragment ***always and absolutely*** comprises amino acid sequence 17-36 and/or 59-84. As long as one fragments comprises the recited fragments, the cited art anticipate the instant claims.

For reasons of record and set forth above, the rejection stands.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 10, and 11 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Cohen et al* (US 6,043,081), in view of *Katz et al* (US 6,005,004) and *Zuckermann et al* (US 6,468,986).

Claims 1-4 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *WO9608970*, and further in view of *Katz et al* (US 6,005,004) and *Zuckermann et al* (US 6,468,986).

Applicants responded to the two rejection combined, thus, the arguments would be addressed together as following.

Applicants argue that there is no motivation to using the fragments of Vpr recited, or to conjugate a Vpr fragment with a nucleic acid molecule in any of the references,

alone or in combination. Applicants also argue that *Katz* and *Zuckermann* do not teach conjugating a protein to a nucleic acid, and their objective is to gain cell entry, not delivery of the compound to the nucleus of the cell. Applicants also argue that in the present invention, the polycationic amino acid is not used to facilitate the entry of a nucleic acid into a cell, but rather is used to coordinate a nucleic acid with the Vpr fragment, i.e. used as a glue.

The arguments have been fully considered but they are not persuasive for reasons of record and following.

In response to applicant's argument that there is no motivation to using the fragments of Vpr recited, or to conjugate a Vpr fragment with a nucleic acid molecule in any of the references, alone or in combination, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

As to the motivation, both *Cohen* reference and *WO9608970* teach conjugating Vpr with a nucleic acid construct as discussed above. Further, *Katz et al* clearly teach the combination of amino acid (polycationic amino acid) and nucleic acid or oligonucleotides (claims 1 and 5). So does *Zuckermann* (abstract). The two references are also relied on for the means of conjugation, such as covalent bounds, non-covalent bonds, and ionic bound.

With regards to the objectives, since the entry of nucleus first requires the entry of cells, any means that promote cell entry would facilitate the nucleus entry. With regards to the purpose of using the polycationic amino acid, the intended use, i.e. whether it is intended to be used as a glue or as a cell entry facilitator, would not affect the novelty of the product. It is noted that the use of a product for a particular purpose is not afforded patentable weight in a product claim where the body of the claim does not depend on the preamble for completeness but, instead, the structural limitations are able to stand-alone. The MPEP states that,".. IN APPARATUS, ARTICLE, AND COMPOSITION CLAIMS, INTENDED USE MUST RESULT IN A STRUCTURAL DIFFERENCE BETWEEN THE CLAIMED INVENTION AND THE PRIOR ART IN ORDER TO PATENTABLY DISTINGUISH THE CLAIMED INVENTION FROM THE PRIOR ART." *In re Casey*, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02). Additionally, it is noted that the specification fails to teach the purpose of using the polycationic amino acid, whether it is glue or cell permissible peptide.

Accordingly, it is still deemed obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of *Cohen et al or WO9608970* by simply combining a polycationic amino acid in the vpr conjugated nucleic acids, such as antisense oligos and a plasmid, and using any known chemical bonding means as taught by *Katz et al* and *Zuckermann et al* with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to do so because it was known that the addition of the polycationic molecule would enhance intracellular penetration of the therapeutic compound and reduce the degradation of nucleic acids during the

delivery process. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

Claims 28-47 are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

JANICE LI
PATENT EXAMINER

Q. Janice Li
Examiner
Art Unit 1632

QJL
November 17, 2003